

CLAIMS

What is claimed is:

5 1. A method for identifying a compound as a non-competitive inhibitor of a ligand-gated neurotransmitter ion channel receptor comprising:

i) determining the  $\log k'$  for binding of the compound to the ligand-gated neurotransmitter ion channel receptor, or to a subunit thereof;

10 ii) determining the energy of the highest occupied molecular orbital of the compound in eV;

iii) determining the area in  $\text{\AA}^2$  of a plane projection of the compound; and

15 iv) identifying as an effective non-competitive inhibitor a compound exhibiting all of  $\log k'$  from 1.1 to 1.9, an energy of the highest occupied molecular orbital from  $-8.6$  to  $-9.2$  eV and a YZ shadow of 25 to  $50 \text{ \AA}^2$ .

20 2. A method for making a pharmaceutical composition comprising admixing a compound identified by the method of claim 1 with a pharmaceutically acceptable carrier.

25 3. The method of claim 1, in which  $k'$  is determined using docking of a computational model of the compound to a computational model of the luminal channel of the ligand-gated neurotransmitter ion channel receptor.

4. The method of claim 1, in which  $k'$  is determined by chromatography of the compound on an affinity matrix comprising at least one subunit polypeptide of the ligand-gated neurotransmitter ion channel receptor.

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5. The method of claim 1, in which the ligand-gated neurotransmitter receptor has a subunit stoichiometry ranging from  $(\alpha)_5(\beta)_0$  to  $(\alpha)_2(\beta)_3$ , or  $(\alpha)_2\beta\delta\gamma$ .

5 6. The method of claim 5, in which the stoichiometry is  $(\alpha)_2(\beta)_3$ .

7. The method of claim 6, in which the model of the luminal channel of the ligand-gated neurotransmitter ion channel receptor has the atomic coordinates of the  $\alpha_3\beta_4$  subtype receptor or the  $\alpha_3\beta_2$  subtype receptor  
10 shown in Appendix 4 or Appendix 5, respectively.

8. A compound that is a derivative of dextromethorphan having the nitrogen-bound methyl group substituted by a  $C_{1-6}$  alkyl group bearing a hydrogen-bond accepting group.  
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9. The compound of claim 8, in which the hydrogen bond accepting group is a keto group, a guanidinium group or a nitrogen-containing heterocyclic group.

20 10. The compound of claim 9, in which the nitrogen-containing heterocyclic group is a pyrrolidine, imidazolidine, piperidine, hexahydropyrimidine or pyrimidine group.

11. A compound comprising  
25 a hydrophobic group comprising a saturated or unsaturated alkyl chain containing 4 to 10 carbon atoms, a saturated hydrocarbon ring containing 5 or 6 carbon atoms, or at least one ring that includes at least two conjugated unsaturated bonds, said ring optionally being fused to additional rings to form a ring system and said additional rings optionally  
30 including one or more hetero atoms;

a hydrogen bond accepting group selected from the group consisting of a keto group, a nitrogen-containing heterocyclic group and a guanidinium group;

5 a linker joining said hydrophobic group and said hydrogen bond accepting group and comprising 1 to 4 carbon atoms and optionally containing an oxygen or sulfur atom;

the compound having activity as a non-competitive inhibitor of  $Rb^+$  efflux of a ligand-gated neurotransmitter ion channel receptor with an  $IC_{50}$  of less than 10  $\mu M$ .

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12. The compound of claim 11, in which the ring is a planar, aromatic ring system.

13. The compound of claim 11, in which the ring is selected from the  
15 group consisting of a phenyl ring, a naphthyl ring, morphinan and dibenzo [1.4] diazepine.

14. A computer system comprising:

20 i) a memory storing positional data of the atomic coordinates of the transmembrane portion of at least one subunit of a ligand-gated neurotransmitter receptor protein; and

25 ii) a processor generating a molecular model having a three dimensional shape representative of a luminal domain portion of the ligand-gated neurotransmitter receptor having a stoichiometry of  $(\alpha)_2(\beta)_3$  based the positional data.

15. The computer system of claim 14, in which the  $\alpha$  subunits are  $\alpha 3$  subtype and the  $\beta$  subunits are  $\beta 2$  or  $\beta 4$  subtype.

30 16. A method for treating Tourette's syndrome, schizophrenia, a cognitive disorder, pain, anxiety, depression, neurodegeneration or an

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addiction caused by an overactive ligand-gated ion channel receptor, comprising administering to a subject an amount of a compound of claim 11 effective to inhibit ion flux through said ligand-gated ion channel.